429, May 1991). Different types of acetylcholine receptors are found in different tissues and respond to different agonists. One type, the nicotinic acetylcholine receptor (nAChR), responds to nicotine. A subgroup of that type is found only in neurons and is called the neuronal nAChR.

REMARKS

Applicants respectfully request reconsideration of this application in view of the following remarks. Claims 40-58 are pending in this application.

Page 2 of the Office Action indicates that the previous amendment to the specification was not entered because it did not comply with the new amendment practice under 37 C.F.R. § 121. Applicants have amended the specification in compliance with 37 C.F.R. § 1.121 by replacing the entire paragraph. A copy of the paragraph with the amendment indicated can be found in the Appendix.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 40-58 under 35 U.S.C. § 112, first paragraph, for the reasons of record. (Paper No. 9, page 2.) The Office asserted that the specification lacks guidance regarding how to make and use a transgenic mouse with a promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor that directs neuronal expression of a heterologous polypeptide selected from a toxin, growth factor, or oncogenic, tumorigenic, or immortalizing protein. Applicants respectfully traverse this rejection.

In Paper No. 5, the Office acknowledged that the specification enables one of skill in the art to make and use a transgenic mouse with a promoter sequence of the β2-subunit of neuronal

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

nicotinic acetylcholine receptor that directs expression of a heterologous ***reporter gene*** in a tissue-specific manner.[1] (Id. at 3-4.) Despite this admittedly enabling disclosure, the Office takes the position that simply replacing the heterologous reporter gene with a different heterologous sequence, such as a heterologous sequence encoding a toxin, growth factor, or oncogenic, tumorigenic, or immortalizing protein, would require undue experimentation.

In Paper No. 5, the Office relied on three references, Palmiter et al., Kappel et al., and Cameron in an attempt to demonstrate that the art of transgenic animals was unpredictable. More specifically, citing a ***1991*** Palmiter et al. reference, the Office asserted that the two most common problems with cell-specific gene expression are "inappropriate expression patterns and failure to achieve adequate expression levels." (Paper No. 5, page 5.) The Office also cited a ***1992*** reference, Kappel et al., for its teaching that "inherent cellular mechanisms may alter the pattern of gene expression." (Id.) Finally, the Office relied on a passage of Cameron (1997) to further support its position that transgene expression is unpredictable. Although the Cameron reference was published in 1997, all the references cited in this passage about transgene regulation and expression (i.e., references 52-60) were published in or before ***1988***—more than six years before applicants' filing date. Thus, as explained in the previous response, none of the references cited by the Office, Palmiter et al., Kappel et al., or Cameron, accurately represents the state of the transgenic art as of applicants' December 14, **1994**, filing date.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

[1] Despite this acknowledgement, the Office continues to reject claims 51, 52, 56, and 57, directed to processes for producing a neuronal host cell that expresses a heterologous reporter gene.

Furthermore, applicants submitted two references, Aguzzi et al. and Camper et al., dated January 1994 and January 1995, respectively, that more closely reflect the state of the art as of the filing date of the instant application. As explained in the previous response, Aguzzi et al. and Camper et al. demonstrate that by late 1994, it was well within the skill of the art to direct tissue-specific expression of genes in transgenic mice using tissue-specific promoters, including neuron-specific promoters. In addition, these references show that as of 1994, those skilled in the art were using these transgenic mice to direct tissue-specific expression of genes encoding toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins and that such transgenic mice could be used, for example, to develop disease models, to develop cell lines, or to gain a better understanding of tissue-specific gene expression.

Relying on Aguzzi et al. and Camper et al. to demonstrate the state of the art as of December 1994, applicants argued that given applicants' disclosure of a novel promoter sequence, and the use of this promoter sequence in a transgene construct to direct neuron-specific expression of heterologous reporter genes, it would not require undue experimentation for one of skill in the art to replace the reporter gene in the transgene construct with other heterologous sequences. While the Office acknowledged applicants' arguments based on Aguzzi et al. and Camper et al. in Paper No. 9, the Office never addressed them. (Paper No. 9, pages 3-4.) Thus, applicants' arguments stand unrebutted.

At page 5 of the Final Office Action, the Office summarily concludes that Aguzzi et al. and Camper et al.:

> do not provide sufficient guidance for one of skill in the art to know whether broadly claimed transgene constructs will be

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

> expressed in the mice at a suitable level to obtain a phenotype, what the phenotype would be, and how the skilled artisan would use the generated transgenic mouse in a disease model system, or what the phenotype of cells isolated from the transgenic mouse would be *in vitro*. The skilled artisan would not know how to use the claimed invention without further characterizing the generated mice or cells. Moreover, it is not readily apparent from the references of Aguzzi et al. and Camper et al. whether any transgene construct, and more particularly, applicants' construct would function to, for example, ablate neurons, or result in a transgenic animal which would be suitable as a disease model.

(Paper No. 9, page 5.) The Office, however, provides no technical reasons to support these assertions. See M.P.E.P. § 2164.04 ("References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. However, specific technical reasons are always required.") (citations omitted). Moreover, once again, the Office appears to have overlooked the arguments presented in applicants' previous response that specifically address these issues.

For example, the Office argues that Aguzzi et al. and Camper et al. do not provide sufficient guidance for one of skill in the art to determine the phenotype of the transgenic mouse and to use the transgenic mouse in a disease model system. (Paper No. 9, page 5.) But applicants have previously shown that as of applicants' filing date, identifying a phenotype would not require undue experimentation. For example, Camper et al. discuss transgene ablation studies in which various toxin genes, including diptheria toxin A, ricin A, and herpes simplex virus thymidine kinase, were linked to different promoters and used to make transgenic animals. Similarly, applicants' transgene construct having the promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor could be used to target expression of the toxin to specific cells, such as the subsets of neuronal cells identified in applicants' specification.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(Specification, pages 38-40.) These transgenic animal would have an identifiable phenotype based on the targeted ablation of the desired cells.

In addition, correlations were known to exist between heterologous proteins and specific diseases. For example, Aguzzi et al. describe a correlation between various heterologous proteins and specific disease states, including the SV40 T antigen and leukodystrophy (pages 11-12), JC viral antigens and leukoencephalopathy (page 12), neurofilament light and heavy chains and amyotrophic lateral sclerosis and infantile spastic muscular atrophy (page 12), proteins encoded by *c-mos* and *v-mos* oncogenes and neurodegeneration (page 13), and CuZn-superoxidase dismutase and neurodegeneration (pages 13-14). Thus, as of applicants' filing date, correlations were known to exist between heterologous proteins and specific diseases. Based on these known correlations, it would not require undue experimentation to identify a particular phenotype and link such a phenoptype to a disease model system.

Moreover, the utility of the claimed transgenic mice is not limited to the development of a disease model system. For example, the skilled artisan would recognize that applicants' claimed transgenic mouse, expressing an oncogenic, tumorigenic, or immortalizing protein, could be used to develop neuronal cell lines, as explained in the specification. (Specification, page 6, lines 12-15.) This is also consistent with the teaching of Camper et al., which describe using cell-specific promoters to direct cell-specific expression of immortalizing oncogenes, such as the SV40 T-antigen, in transgenic mice. (Camper et al., page 247, last paragraph.) These mice are useful for developing immortalized cell lines that can be used, for example, to identify cell-specific transcription factors or to examine gene expression. (Id.)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The Office also argues that Aguzzi et al. and Camper et al. do not provide sufficient guidance for one of skill in the art to know whether the claimed transgene constructs will be expressed at suitable levels to obtain a phenotype. (Paper No. 9, page 5.) Previously, applicants argued that determining an appropriate nonlethal expression level is a matter of routine screening and does not amount to undue experimentation. One of skill in the art would be prepared to screen negative transgenic mice to find one with the desired phenotype. Cf. In re Wands, 858 F.2d 731, 740, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988) (finding that practitioners are prepared to screen negative hybridomas in order to find one that makes the desired antibody).

Finally, without explanation, the Office concludes that "it is not readily apparent from the references of Aguzzi et al. and Camper et al. whether any transgene construct, and more particularly, applicants' construct would function to, for example, ablate neurons, or result in a transgenic animal which would be suitable as a disease model." (Paper No. 9, page 5). As acknowledged by the Office in Paper No 5, applicants used their novel promoter sequence in a transgene construct to direct neuron-specific expression of heterologous reporter genes. Aguzzi et al. disclose well-characterized transgene constructs containing other neuron-specific promoters operatively linked to toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins. (Aguzzi et al., Abstract, Table 1.) These transgene constructs were used to make transgenic mice that serve as models of neurological disease. (Id.) In addition, Camper et al. demonstrate that one of skill in the art could readily achieve targeted cell ablation using trangenic animals having a cell-specific promoter linked to a toxin gene. Thus, as of applicants' effective U.S. filing date, December 14, 1994, sequences encoding heterologous proteins,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

including toxins, growth factors, and oncogenic, tumorigenic, or immortalizing proteins, were well known. Moreover, as shown in Aguzzi et al., the skilled artisan knew how to use these heterologous sequences in transgene constructs to direct neuron-specific expression of heterologous proteins. Therefore, as of applicants' filing date, it would not require undue experimentation to incorporate a heterologous sequence, such as one of those disclosed in Aguzzi et al. or Camper et al., into applicants' transgene construct having the promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor gene. Accordingly, given applicants' disclosure coupled with what was known in the art, the skilled artisan could combine applicants' novel promoter sequence with known heterologous sequences to generate transgenic mice without undue experimentation.

For the reasons discussed above, the specification provides an enabling disclosure that is commensurate in scope with the claimed subject matter. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 43 and 44 under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. (Paper No. 9, page 6.)

Specifically, the Office asserted that claim 43 is rendered vague and indefinite by the phrase "the DNA of the second mouse is not identical to the DNA of the first mouse." (Id.) According to the Office, it is unclear whether the term DNA refers to endogenous DNA or the transgene. (Id.) Applicants respectfully traverse this rejection.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

According to the plain meaning of the phrase in question, the DNA of the second mouse has some difference in nucleotide sequence compared to the DNA of the first mouse. The difference in nucleotide sequence could be in the endogenous DNA of the mice or it could be in the transgene, or it could be in both. The meaning of this claim language is clear. Thus applicants respectfully request withdrawal of this rejection.

The Office rejected claim 44 asserting that it is unclear if the DNA sequence is referring to the transgene or to endogenous DNA. (Paper No. 9, page 6.) Applicants respectfully traverse this rejection.

Claim 44 recites that the "the second mouse is a transgenic mouse containing *a DNA sequence* different from *the DNA sequence* of the first mouse." Claim 44 depends indirectly from claim 41. Since claim 41 describes a first mouse containing "a DNA sequence comprising ..." the term "the DNA sequence of the first mouse" in claim 44 refers back to the DNA sequence recited in claim 41. Therefore, the second mouse of claim 44 has a DNA sequence that is different from the DNA sequence of the first mouse. Applicants respectfully request withdrawal of this rejection.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Double Patenting Rejection

The Examiner acknowledged applicants' request to hold the provisional double patenting rejetion in abeyance until Application No. 08/465,712 issues as a patent. (Paper No. 9, page 6.)

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account no. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: August 30, 2001

By: _____
Timothy B. Donaldson
Reg. No. 43,592

Tel: (202) 408-4000
Fax: (202) 408-4400
Email: timothy.donaldson@finnegan.com

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000